

Online Research @ Cardiff

This is an Open Access document downloaded from ORCA, Cardiff University's institutional repository: <https://orca.cardiff.ac.uk/id/eprint/133296/>

This is the author's version of a work that was submitted to / accepted for publication.

Citation for final published version:

Carey, Elinor Claire, Gardiner, Andrew Talbot Charles, Adams, Robert John, Farnell, Damian Joseph John ORCID: <https://orcid.org/0000-0003-0662-1927>, Claydon, Nicholas Charles ORCID: <https://orcid.org/0000-0002-4151-1515> and Thomas, David William ORCID: <https://orcid.org/0000-0001-7319-5820> 2021. The effects of age and sex on mandibular bone graft donor sites. Oral Surgery 14 (1) , pp. 52-58. 10.1111/ORS.12535 file

Publishers page: <http://dx.doi.org/10.1111/ORS.12535>
<<http://dx.doi.org/10.1111/ORS.12535>>

Please note:

Changes made as a result of publishing processes such as copy-editing, formatting and page numbers may not be reflected in this version. For the definitive version of this publication, please refer to the published source. You are advised to consult the publisher's version if you wish to cite this paper.

This version is being made available in accordance with publisher policies.

See

<http://orca.cf.ac.uk/policies.html> for usage policies. Copyright and moral rights for publications made available in ORCA are retained by the copyright holders.



ORIGINAL ARTICLE

The effects of age and sex on mandibular bone graft donor sites

E.C. Carey¹, A.T.C. Gardiner, R.J. Adams , D.J.J. Farnell , N.C. Claydon  & D.W. Thomas 

School of Dentistry, Cardiff University, Cardiff, UK

Key words:

CBCT, donor site, grafting, implant bone, mandible, ageing, sexual dimorphism

Correspondence to:

RJ Adams

School of Dentistry

Cardiff University

Cardiff

UK

Tel.: 0044 2920 744252

email: adamsr6@cardiff.ac.uk

¹Present address: Prince Charles Hospital, Merthyr Tydfil, UK

Accepted: 7 June 2020

doi:10.1111/ors.12535

Abstract

Objectives: Intra-oral bone grafting relies on three-dimensional understanding of mandibular anatomy. This study assessed the bone volume at the two most common intra-oral bone harvesting sites, the retromandibular and symphyseal regions, and assessed the impact of age and sex on the available bone at these sites.

Materials and methods: Demographic and anatomical data were collected from cone beam computer tomographs (CBCT's) of 200 randomly selected, fully dentate participants (100 male/100 female) between the ages of 24 and 86 years. Statistical analysis was conducted with SPSS V25, using ANalysis of COVariance (ANCOVA) to determine the effects of age and sex on the measurements at the donor sites.

Results: At retromandibular sites, women have a broader alveolar crest with a narrower mandible at the level of the IDC. There is a statistically significant difference, between the sexes, in bone width from the buccal cortex to the IDC. Men have a significantly greater distance from the outer buccal plate to the IDC. There is no difference in any measured dimension at the symphyseal region. There is a statistically significant reduction in bone volume with increasing age at both mandibular sites of 0.03–0.05 mm annually, irrespective of tooth loss.

Conclusion: Anatomical variability due to sex and bone reduction with age are both important findings in dental implantology, which must be considered when treatment planning and selecting bone grafting sites in the mandible. This study reinforces the importance of pre-operative CBCT in planning bone grafting procedures.

Clinical Relevance

Scientific rationale for study

Autogenous bone grafting is an essential procedure in dental implantology and oral surgery. Common intra-oral donor sites include the mandibular symphysis¹ and retromandibular regions². The available bone volume, at these sites, will be restricted by the individual anatomy and proximity of underlying vital structures³. A previous CBCT study⁴ has demonstrated the degree of anatomical variation

present at these important donor sites. However, few studies have investigated this variation in relation to age and sex at graft donor sites in the mandible.

Principle findings

This study has demonstrated differences between the sexes, in bone volume, at the common intra-oral donor sites. It also identified an overall reduction in bone volume with time that is not related to tooth loss.

Practical implications

This study highlights the need for three-dimensional imaging prior to the consideration of intra-oral bone grafting procedures.

Introduction

Intra-oral bone is an important fabric in oral surgery for bone grafting procedures. The mandible is often selected as a donor site due to its wealth of intramembranous bone that is reported to show minimal resorption and predictable bone density, compared to endochondral bone grafts^{5–8}. It also offers ease of accessibility and low morbidity^{9–11}. All bone grafting techniques report good implant cumulative survival rates^{12,13}, although implant survival is not a direct measurement of graft success. A previous study⁴ demonstrated large variability in volume at mandibular donor sites. This study focuses on the variation at mandibular bone graft donor sites based on gender and age.

Aims and objectives

The aim of the study was to assess the effect of sex and age on the anatomical variation of intra-oral bone harvesting sites. The objectives of the study were to: measure the bone volume at the mandibular symphysis and retromandibular donor sites and determine whether age- or sex-specific differences were apparent in available bone volume.

Materials and methods

In this retrospective study, cone beam computer tomographs (CBCTs) were assessed in 200 randomly selected participants (100 male/100 female; between the ages of 24 and 86 years) in a single implant centre in Cardiff, UK. The CBCT scans were taken as part of patient's assessment for dental implant treatment, using the Sirona GALILEOS CBCT Scanner system.

Inclusion and exclusion criteria

Inclusion

Retromandibular region: intact upper and lower posterior dentition to the second molar teeth with absent lower third molar teeth. Symphyseal region: Presence of upper and lower anterior teeth and lower premolars.

Exclusion

Retromandibular region: Presence of pathology (e.g. periodontal disease, cysts etc.), supra-eruption of the lower second molars. Symphyseal region: Presence of mandibular tori, presence of pathology (periodontal disease, cysts etc.).

All scans were anonymised prior to the study and the CBCT data was analysed by a single investigator. Demographic information and the anatomical measurement of the inferior alveolar nerve and the mandibular cortices were collected. The symphysis and retromandibular anatomy were recorded using pre-defined criteria shown below. Statistical analysis of the data was performed using SPSS V25 to study the relationship of these anatomical variables to patient age and sex.

Statistical analysis

As comparison of sex is confounded by age, analysis of covariance (ANCOVA) was employed to characterise the effects of age (a continuous covariate) and sex (a binary factor), allowing determination of the effects of both sex (adjusted for age) as well as the changes/gradient (both sexes) with respect to age on the distance measurements. Furthermore, an interaction term (i.e. age \times sex) was included in the model to determine if the changes with age (i.e. the gradients of the regression lines) were different for males versus females. The generalised linear model (GLM) command was used in SPSS V25 in order to perform these calculations and residuals were found to be normally distributed for this model, as required.

Radiographic data analysis

Retromandibular measurements and positions are shown in Fig. 1. For standardisation, a fixed reference point was chosen 10 mm distal to the lower second molar tooth on the alveolar crest. A coronal slice at this position was used for analysis of the distance of the IDC from the outer buccal cortex (AB) and the width of mandible at the level of the IDC (BC). The greatest width of the alveolar crest (DE) at the level of the lower second molar was also measured. Symphyseal measurements included the width of mandible at the canine (FG) and the midline (HI).

Results

About 50 male and 50 female cases were studied at each of the two sites. A considerable variability in

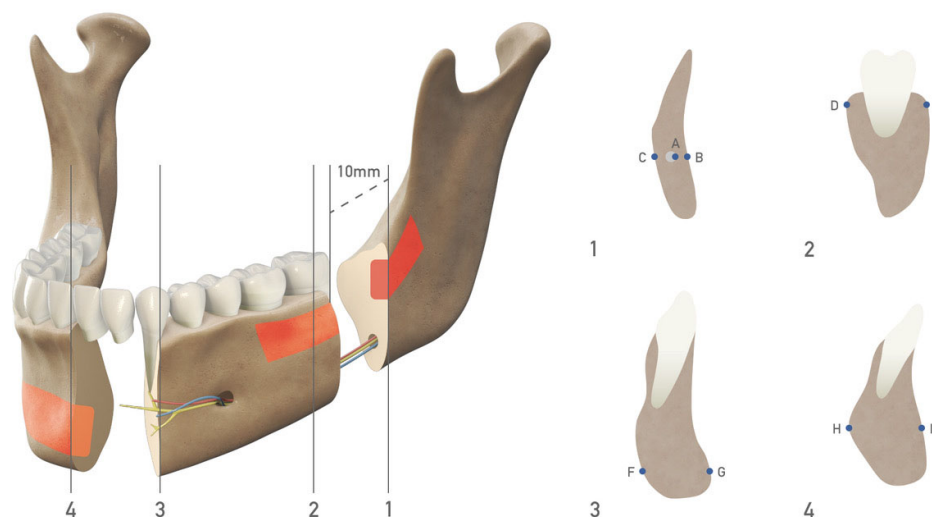


Figure 1 Reference points for mandibular measurements.

mandibular anatomy at bone grafting sites was observed (Table 1 and Table 2).

Retromandibular region

The mean width of the mandible was 7.9 mm (4.61–14.27 mm). The mean distance from the buccal plate to the IDC was 3.5 mm (1.02–7.92 mm).

Age

Thinning at the width of the alveolar crest [DE] was observed with age ($P = 0.002$), estimated at a reduction of 0.033 mm per year (both sexes). However, this bone loss associated with age was more marked in females than males for DE ($P = 0.034$) with females having a gradient that was 0.045 mm per year steeper than in males. The distance from the buccal plate to the ID canal [AB] also revealed a significant reduction with age ($P < 0.001$), calculated at 0.036 mm annually (both sexes). This reduction with age was significantly more marked in males than females in this case ($P < 0.001$), with males having a gradient that was 0.072 mm per year steeper than in females. A significant annual reduction in the width of the

mandible at the level of the IDC [BC]. The change was observed in both male and female subjects. An overall decrease of 0.046 mm of bone was seen each year (male and female genders) at this location ($P < 0.001$). The bone loss with age was significantly more marked in males than females in this case ($P < 0.001$), with males having a gradient that was 0.082 mm per year steeper than in females.

Sex

Statistically significant differences between females and males were observed in the retromandibular region, where, for example, females are wider at the alveolar crest [DE] by 2.19 mm ($P = 0.074$) compared to males. From the IDC to the buccal plate [AB], males are wider by 4.29 mm ($P < 0.001$) compared to females. The width of the mandible at the level of the IDC at the second molar [BC] was significantly wider in males than in females by 4.59 mm ($P < 0.001$).

Symphyseal region

Symphysis

Table 1 Analysis of the retromandibular region

Measurement	Min (mm)	Max (mm)	Mean distance – all subjects (mm)	<i>P</i> value	Annual bone reduction with age (mm)	<i>P</i> value
AB – Distance – Buccal plate to IDC	1.02	7.92	3.44	<0.001	0.036	<0.001
BC – Width of mandible at level of IDC	4.61	14.27	7.92	<0.001	0.046	<0.001
DE – Width of alveolus at crest	10.19	18.20	13.66	0.074	0.033	0.002

Table 2 Analysis of the symphyseal region

Measurement	Min (mm)	Max (mm)	Mean distance – all subjects (mm)	P value	Annual bone reduction with age (mm)	P value
FG – Width of mandible at canine site	7.66	14.85	11.46	0.479	0.037	0.001
HI – Width of mandible at midline	11.24	16.39	13.75	0.257	0.026	0.005

Age. ANCOVA demonstrated a significant reduction in the width of mandible at the canine site [FG] with age ($P = 0.001$), given by 0.037 mm per year (both sexes).

An annual reduction in the width of mandible at the midline [HI] of 0.026 mm ($P = 0.005$) was evident.

Sex. ANCOVA demonstrated that females have a narrower mandibular width in the midline [HI] by 1.079 mm ($P = 0.257$) and narrower mandibles at the canine sites [FG] by 0.859 mm ($P = 0.479$) when compared to males. Thus, ANCOVA suggested that these differences were not significant ($P > 0.05$). In both cases, there were no statistically significant differences in the gradients with age between males and females ($P > 0.05$).

Discussion

Dimensional requirements of an autogenous block bone graft

Mandibular autogenous grafts are primarily composed of cortical bone. They present predictable resorption patterns, minimal morbidity and ease of access. Misch⁷ described the optimal landmarks for the retromandibular block donor site graft. The initial osteotomy for retromandibular bone harvest is approximately 3–5 mm medial to the external oblique ridge, where adequate thickness develops. Beneath the cortex is the inferior dental canal (IDC) and its contents. Many studies^{14–17} have attempted to quantify safe volumes and ideal zones for retromandibular grafts, but an agreed safe harvesting thickness remains undecided. A study by Zhang *et al.*¹⁴ suggested a mean harvestable graft dimension of 15.5 × 3.2 mm (height × thickness) in males and 14.1 × 2.9 mm in females. Two further studies^{16,17}, with similar findings, report the 'safe thickness' of a mandibular ramus graft as 2.5–3.0 mm across all ages and sexes. This study supports these findings, demonstrating a mean thickness of 3.5 mm bone before encountering the IDC across both genders. In

this study, however, the minimum bone-thickness buccal to the IDC was 1.02 mm. This reinforces the importance of pre-operative CBCT planning in order to prevent possible trigeminal nerve injury.

Numerous anatomical studies have attempted to investigate the development of the mandible and its remodelling with age^{18–22}. Changes in the shape of the mandible with age are well-described in association with growth, age and disease. These changes are apparent in both the tooth-bearing alveolus as well as in the ramus and angles of the mandible (in overall length and height). In a cadaveric study, Parr *et al.*¹⁸ proposed that the observed changes in mandibular shape, and remodelling, were principally related to ante-mortem tooth loss. They noted that the mandible is rich in muscle attachments and the morphology of the mandible at these attachment zones is dependent on the presence of teeth and the load on bone through mastication. The adaptation and remodelling seen in the aged mandibles were linked directly to tooth-loss rather than the process of ageing concluding that few mandibular measurements exhibit specific age-related changes. Shaw¹⁹ attempted to document the age-related changes in the mandible (ramus height, body height and body length) in both sex and described an age-dependent increase in mandibular angle which was independent of sex. Their study excluded edentulous patients, to negate the effects of tooth-loss, but included both dentate and partially dentate subjects, making the effects of ageing versus those of ante-mortem tooth loss difficult to determine. The use of CBCT in dentate subjects in our study overcoming these limitations. Whilst a similar study by Zhang *et al.*¹⁴, failed to demonstrate any age-related changes in retromandibular graft sites. Their study included 59 subjects with CBCT analysis. In addition to sample size, the study we report here included only patients with intact dentitions. Excluded individual patients with missing posterior teeth, may also aid in eliminating potential bias.

The biological basis of the age-dependent morphological changes we have observed in dentate subjects has been hypothesised to relate to age-dependent

changes in vascularisation. Wu *et al.*²⁰ were able to demonstrate that ageing is associated with peripheral nerve degradation, reduced blood supply and bone destruction in the mandible. Their study showed changes in mandibular bone metabolism following sensory denervation observed in ageing populations. Gradual peripheral denervation and narrowed blood vessel diameter occurs with advancing age²¹ and, therefore, may be responsible for a gradual 'thinning' of bone.

Age-related hormonal changes have also been postulated to influence bone metabolism and remodelling of the mandible. It is a well-documented phenomenon, particularly in postmenopausal women. Mandibular radiography has been employed as a screening tool for osteoporosis, due to the reliable pattern of age-related cortical thinning associated with lowered oestrogen levels²². Whilst these mechanisms could clearly explain, in part, the volume loss observed in the female population in our study, our results in both sexes demonstrated similar patterns and rates of bone-loss at both sites, even though the oestrogen-related demineralisation is not usually observed in both sexes.

Sex dimorphism in the mandible

A large number of osteological and anatomical studies that examine dimorphism of the mandible, including a recent systematic review by Hazari *et al.*²³. Their study reviewed various parameters of the mandible observed in the last 15 years for sex dimorphism. They reported on the findings of 16 radiographic and 14 morphometric cadaver studies which overwhelmingly supported the statistically significant dimorphism seen in the mandible²³. Recognised markers for sex dimorphism include: increased ramus height and breadth, increased mandibular bigonial width and increased bicondylar width in males. The ramus flexure is also a recognised marker for sex dimorphism. Again, no anatomical studies specifically measured the areas reported in our study.

At the retromandibular region, our study demonstrated that female subjects had a significantly greater alveolar width. This is not believed to be related to the tooth-size^{24,25}. Whilst males have typically larger molar crowns than females²⁴, Coquerelle²⁵ argues that sexual dimorphism in the mandible is not associated with the teeth, but instead is related to hormonal inputs and muscular attachments. Muscles inserting into the alveolar aspect of the retromandible include the masseter,

mylohyoid and buccinators. The buccinators have the closest attachments to the retromandibular alveolus, and they are reported as being more developed in females²⁶.

Our study also reported that males have a wider mandible at the level of the IDC and a thicker buccal plate protecting the IDC. Many anatomical studies^{14,27–32} support this statistically significant gender difference. Some studies have attempted to correlate these findings with conditions of the bone, masticatory forces, skeletal patterns, dental occlusion and hormonal changes^{33–36}) as all of these are hypothesised to influence mandibular bone morphology. These theorise that each of the above may modify the thickness and density of the bone either directly or indirectly, by influencing muscular actions, in turn altering bone morphology. To date however, none of these theories, however, have been conclusively proven.

Other similar CBCT studies at mandibular graft sites

Zhang *et al.*¹⁴ employed CBCT imaging to study the alveolar ridge in the posterior mandible to estimate a safe graft size, and how this related to dental status, gender and age in 59 cases (*vide supra*). Zhang's findings on one hand contrasted with our data, reporting that males demonstrated larger alveolar volumes than females at the retromandibular graft sites, their demonstration that males had a significantly thicker buccal plate overlying the IDC were consistent with those reported here.

Whilst this is the largest study of its type, the study remains relatively small in sample size. Moreover, the retrospective nature of the study did not afford the opportunity to accurately identify all local and systemic factors which may explain these findings. Future studies should include a record of ethnicity, skeletal class, medical history (particularly bone-related conditions e.g. osteoporosis, myeloma, hyperparathyroidism), mandibular trauma and prior exposure to medications influencing bone deposition/resorption for example, glucocorticoids, and anti-resorptive drugs. Whilst an apparent limitation of this study was the selection of an arbitrary position/site at which to measure the dimensions of the alveolus (10mm distal to the ACJ) of the lower second molar) this allowed us inter-sample standardisation. As no previous studies of this nature were available, no unified agreed protocol for positioning measurement for mandibular bone grafts of the retromandibular region existed.

Conclusion

This study has demonstrated a considerable anatomical variation at bone harvesting sites and describe the sex-dependent differences at the retro-mandibular graft site. Significant gender differences in bone width from the buccal plate to the lingual plate at the level of the IDC exist. Men have a greater distance from the outside of the buccal plate to the IDC at the retromandibular site. Women exhibiting a broader alveolar crest, with a narrower mandible at the level of the IDC. At the symphyseal region whilst there were no gender differences, a statistically significant reduction of bone volume at both mandibular sites occurs at a rate of 0.03–0.05mm.

This data demonstrate statistically significant quantitative differences in male and female mandibles at the anatomical landmarks for autogenous bone graft harvesting sites. It documents the statistically significant reductions in bone volume seen with ageing in dentate populations, irrespective of tooth loss. The relevance of these findings to the oral surgeon with respect to surgical planning for harvesting autogenous mandibular grafts is clear. This study confirms the importance of CBCT imaging for treatment planning prior to harvesting bone grafts from these mandibular sites.

Disclosure statements

Miss Carey, Dr. Adams, Dr. Farnell, Dr. Gardiner, Dr Claydon and Prof. Thomas have nothing to disclose.

Acknowledgements

Evidence search: Changes in the shape of the mandible with age and sex. Rhys Whelan. (12th July, 2019). Swansea, UK: Bwrdd Iechyd Prifysgol Bae Abertawe Library Services.

References

- Misch CM, Misch CE, Resnik RR, Ismail YH. Reconstruction of maxillary alveolar defects with mandibular symphysis grafts for dental implants: a preliminary procedural report. *Int J Oral Maxillofac Implants* 1992;7:360–6.
- Misch CM. Comparison of intraoral donor sites for onlay grafting prior to implant placement. *Int J Oral Maxillofac Implants* 1997;12:767–76.
- Clavero J, Lundgren S. Ramus or chin grafts for maxillary sinus inlay and local onlay augmentation: comparison of donor site morbidity and complications. *Clin Implant Dent Relat Res* 2003;5:154–60.
- Adams RJ, Hamid L, Binney A, Claydon N, Farnell D, Griffiths B *et al* A radiographic analysis of anatomical variation at the mandibular sites of intraoral bone harvesting. *Br J Oral Surg* 2018;11:105–11.
- Koole R, Bosker H, van der Dussen FN. Late secondary autogenous bone grafting in cleft patients comparing mandibular (ectomesenchymal) and iliac crest (mesenchymal) grafts. *J Craniomaxillofac Surg* 1989;17(suppl 1):28–30.
- Kusiak JF, Zins JE, Whitaker LA. The early revascularization of membranous bone. *Plast Reconstr Surg* 1985;76:510–6.
- Misch CM. Use of the mandibular ramus as a donor site for onlay bone grafting. *J Oral Implantol* 2000;26:42–9.
- Moskalewski S, Osiecka A, Malejczyk J. Comparison of bone formed intramuscularly after transplantation of scapular and calvarial osteoblasts. *Bone* 1988;9:101–6.
- Braun TW, Sotereanos GC. Autogenous regional bone grafting as an adjunct in orthognathic surgery. *J Oral Maxillofac Surg* 1984;42:43–8.
- Misch CM, Misch CE. The repair of localized severe ridge defects for implant placement using mandibular bone grafts. *Implant Dent* 1995;4:261–7.
- Sindet-Pedersen S, Enemark H. Reconstruction of alveolar clefts with mandibular or iliac crest bone grafts: a comparative study. *J Oral Maxillofac Surg* 1990;48:554–8.
- Aghaloo TL, Moy PK. Which hard tissue augmentation techniques are the most successful in furnishing bony support for implant placement? *Int J Oral Maxillofac Implants* 2007;22(suppl):49–70.
- Al-Nawas B, Schiegnitz E. Augmentation procedures using bone substitute materials or autogenous bone - a systematic review and meta-analysis. *Eur J Oral Implantol* 2014;7(Suppl 2):19–34.
- Zhang W, Tullis J, Weltman R. Cone beam computerized tomography measurement of alveolar ridge at posterior mandible for implant graft estimation. *J Oral Implantol* 2015;41:231–7.
- Hwang KG, Shim KS, Yang SM, Park CJ. Partial thickness cortical bone graft from the mandibular ramus: a non-invasive harvesting technique. *J Periodontol* 2008;79:941–4.
- Leong DJM, Li J, Moreno I, Wang H. Distance between external cortical bone and mandibular canal for harvesting ramus graft: a human cadaver study. *J Periodontol* 2010;81:239–43.
- Verdugo F, Simonian K, McDonald RS, Nowzari H. Quantitation of mandibular ramus volume as a source of bone grafting. *Clin Impl Dentistry and Related Res* 2009;11:32–7.

18. Parr NM, Passalacqua NV, Skorpinski K. Investigations into age-related changes in the human mandible. *J Forensic Sci* 2017;62:1586–91.
19. Shaw RB. Aging of the mandible and its aesthetic implications. *Plast Reconstr Surg* 2010;125:332–42.
20. Wu Q, Yang B, Cao C, Guang M, Gong P. Age-dependent impact of inferior alveolar nerve transection on mandibular bone metabolism and the underlying mechanisms. *J Mol Histol* 2016;47:579–86.
21. McGregor AD, MacDonald D. Age changes in the human inferior alveolar artery – a histological study. *Br J Oral Maxillofac Surg* 1989;27:371–4.
22. Roberts M. Changes in mandibular cortical width measurements with age in men and women. *Osteoporosis Int* 2011;22:1915–25.
23. Hazari P, Hazari RS, Mishra SK, Agrawal S, Yadav M. Is there enough evidence so that mandible can be used as a tool for sex dimorphism? A systematic review. *J Forensic Dent Sci* 2016;8:174.
24. Schwartz GT. Sexual dimorphism in modern human permanent teeth. *Am J Phys Anthropol* 2005;128:312–7.
25. Coquerelle M. Sexual dimorphism of the human mandible and its association with dental development. *Am J Phys Anthropol* 2011;145:192–202.
26. Ellis L, Das S. Sex differences in smiling and other photographed traits: a theoretical assessment. *J Biosoc Sci* 2010;43:345–51.
27. Kane AA, Lo LJ, Chen YR, Hsu KH, Noordhoff MS. The course of the inferior alveolar nerve in the normal human mandibular ramus and in patients presenting for cosmetic reduction of the mandibular angles. *Plast Recon Surg* 2000;106:1162–76.
28. Wadu SG, Penhall B, Townsend GC. Morphological variability of the human inferior alveolar nerve. *Clin Anat* 1997;10:82–7.
29. Zoud K, Doran GA. Microsurgical anatomy of the inferior alveolar neurovascular plexus. *Surg Radiol Anat* 1993;15:175–9.
30. Stein W, Hassfeld S, Muhling J. Tracing of thin tubular structures in computer tomographic data. *Comput Aided Surg* 1998;3:83–8.
31. Svane TJ, Wolford LM, Milam SB, Bass RK. Fascicular characteristics of the human inferior alveolar nerve. *J Oral Maxillofac Surg* 1986;44:431–4.
32. Poirot G, Delattre JF, Palot C, Flament JB. The inferior alveolar artery in its bony course. *Surg Radiol Anat* 1986;8:237–44.
33. Taguchi A, Tanimoto K, Suei Y, Wada T. Tooth loss and mandibular osteopenia. *Oral Surg Oral Med Oral Pathol Oral Radiol Endod* 1995;79:127–32.
34. Taguchi A, Tanimoto K, Suei Y, Otani K, Wada T. Oral signs as indicators of possible osteoporosis in elderly women. *Oral Surg Oral Med Oral Pathol Oral Radiol Endod* 1995;80:612–6.
35. Sies ML, De Farias SR, Vieira MM. Oral breathing: relationship between facial type and dental occlusion. *Rev Soc Bras Fonoaudiol* 2007;12:191–8.
36. Du X. Age-related changes of bone mineral density in mandible by quantitative computed tomography. *J Biol Regul Homeost Agents* 2017;31:997–1003.